# THE HISTORY OF FDA'S BIORESEARCH MONITORING PROGRAM

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Let me start in really ancient times. Prior to 1938 a manufacturer was not required to submit to the agency evidence of drug safety or efficacy before marketing a drug. Any drug could be marketed, and the law merely permitted the government to take action if the drug proved to dangerous or to be misbranded. Like most law in the consumer protection area, the Food, Drug, and Cosmetic Act of 1938 was not passed upon its merits alone. It had been proposed in 1933 as a revision of the 1906 Food and Drugs Act and had been bouncing around, stalled in Congress, when in 1937 the elixir of sulfanilamide tragedy occurred. The manufacturer, in developing a liquid preparation of sulfanilamide found that the sulfanilamide dissolved easily in diethylene glycol. The preparation was tested for appearance, flavor, and fragrance, passed with flying colors, and was marketed. Unfortunately, the diethylene glycol was a poor choice of vehicle and 107 people subsequently died from taking the product. Faced with this, in 1938 Congress quickly passed the stalled Food, Drug, and Cosmetic Act which required that before a new drug was introduced into the market the manufacturer was required to submit to the Food and Drug Administration adequate information including both animal and clinical studies to demonstrate the safety of the drug for its proposed uses. The information required included details concerning the chemistry of the drug, measures to ensure its purity, reproducibility and stability, animal studies to show that

the drug was either safe in single dose or over a period of time, and clinical studies that had been conducted with the drug to establish its safety. This evidence was to be presented in the form of a document which was known as a New Drug Application or NDA.

The early NDAs were rather small and informal documents, but after World War II, with the development of more sophisticated drugs, the NDAs became somewhat more detailed. To review these NDAs, FDA at that time had a total of three physicians. These physicians, in the early 1950s, occasionally wanted to get an independent opinion on the drug they were reviewing rather than depending solely on the rather inadequate NDAs submitted to them, and therefore they might, on an informal basis, visit a clinical investigator to get the clinical investigator's opinion on the drug. Obviously they tried to visit the person who had done the largest and the best study to obtain these opinions. Those physicians whose work was primarily testimonial in character were never visited, and no attempt was made to challenge the work of investigators working for well established drug firms on products that might be expected to be useful additions to the therapeutic armamentarium. All medical officers had their opinions on what drugs might be useful, and what drugs were borderline or clearly fraudulent preparations, and they would look very carefully at the work submitted on these preparations, but in fact very little critical work was submitted

in the NDAs of those days. Remember, no efficacy data were required to be submitted.

By 1960 the New Drug Branch of what was then called the Bureau of Medicine had increased from three to seven full time and four half time physicians, and a concern developed amongst these reviewers that a small stable of clinical investigators was contributing to a great many New Drug Applications in widely ranging fields of medicine, seemingly outside of their fields of competence. It was also recognized that although the sponsor was required to keep a list of all investigators to whom the drug had been supplied, this information was not provided to the FDA, and that the New Drug Application did not necessarily contain data on all the studies that had been done on the drug. As a consequence, in September of 1961 the Office of the Medical Director asked the New Drug Division to maintain a file of clinical investigators "who have contributed incredible reports to NDAs. The investigators should be so patently unbelievable that their very appearance in another application would create suspicion.... It should not contain the names of investigators who simply are substandard, poor reporters, over-enthusiastic, etc.,

Instead, it should contain names of those for whom there is good reason to suspect untruthfulness, psychosis, or dangerous incompetence and irresponsibility."

In mid-1961 the first "investigator investigation" was performed by an FDA medical officer on a Silver Spring, Maryland general practitioner who had taken undertaken multiple clinical studies for more than 25 different drug companies. These studies included a wide variety of products, tested not only on adults, but also on infants and children. Although this investigator had done a large number of studies, he was by no means the most prolific on the list, and it seems that the primary reason he was selected for a visit was that he was a local investigator and was readily available. It was quickly and easy determined that the studies reviewed had in whole or in part not actually been done, most of the results being produced by the physician at his kitchen table filling out report forms. A criminal indictment covering five studies resulted, specifying the knowing and willing submission to the government of false, fraudulent and fictitious reports. The physician pleaded nolo contendre, resulting in a fine, a suspended sentence, and the ultimate loss of his license to practice medicine.

In 1960 a cholesterol lowering agent called MER-29 was approved, and subsequent human use revealed balding, impotence, cataracts and liver damage. Subsequent investigation found that previously

performed animal studies had found liver, reproductive, and ocular toxicity at low doses which had not been reported, and the sponsor and three top scientists of the manufacturer were found guilty of falsifying source data and failing to submit to FDA data which revealed serious toxicity.

On the heels of the MER-29 episode came the thalidomide tragedy, and in 1962 the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act were passed, followed quickly by, in 1963, the implementing Investigational Drug Regulations. Like the 1938 act itself, the amendments and the implementing regulations had been sitting on the shelf with no real motivation for passage until the tragedy occurred. It is interesting to note that unlike most current regulations, the original Investigational Drug Regulations were not written by a committee but were the product of a single individual, a man named Julius Hauser, who in retrospect produced a product that has remained pretty much unchanged through the years, although obviously expanded upon to some extent. In any event, the Investigational Drug Regulations established the IND, and are most remembered for the establishment of the requirement that efficacy as well as safety must be established before a drug may be approved for marketing. But as far as the Bioresearch Monitoring Program is concerned, it is of note that the regulations require the submission to FDA of protocols for the conduct of future human studies, the names of the investigators designated to

conduct those studies, the qualifications of those investigators, and identification the facilities to be used by the investigators who are to undertake those studies.

With the IND Regulations came the establishment of the Investigational Drug Branch whose purpose was to review the newly submitted INDs. Although this seemed to be the thing to do at the time, it established a situation whereby the work done under the IND was reviewed by one group of individuals, and once the study of a drug was culminated in the submission of an NDA, the NDA went to another group of individuals who had no knowledge of the history of the drug investigation and the problems associated with the study of the drug. This situation lasted for about four years. From a Bioresearch Monitoring Program perspective, however, the Investigational Drug Branch was of some importance, since one of its first concerns was that of providing an adequate mechanism for scrutinizing more carefully the work of clinical investigators. A storage and retrieval system was designed to capture information from incoming INDs, including the names and addresses of all clinical investigators. This information was recorded on index cards, one for each investigator, and filed alphabetically by investigator. Thus, it was possible to determine the studies in which a given investigator was named to have participated. The index cards evolved into punch cards, and of course that information is now computerized, and I have reason to

believe that with that computerization came a decrease rather than an increase in the accuracy of the system.

You will recall that I mentioned that in 1961 a request had been made for the establishment of a list of clinical investigators who had contributed incredible reports through (among other things) untruthfulness and irresponsibility. The first "untruthful, irresponsible" clinical investigator visited under the new regulations was visited in 1965. This individual had been listed in 82 INDs for 27 different sponsors. The reason for his inspection, however, was not because of these numbers, but because of a production error. In the study of a hypnotic combination drug containing scopolamine, the pilot plant produced a drug which contained ten times the intended dose. The sponsor reported to FDA the results of two clinical trials with the product, each containing about 20 subjects. One trial was done in prisoner volunteers, the other in patients in a chronic disease hospital. All of the prisoner volunteers displayed in various degrees the manifestations of atropine poisoning, including dry mouth, flushed skin, and excitement. All emphatically refused further participation in the study. In contrast, none of the hospitalized patients showed any ill-effects, and universally satisfactory results were reported. FDA's investigation of the

conduct of this study showed that the conduct of the entire study had been entrusted to a laboratory technician; that at least some of the patients alleged to have been in the trial were either dead or absent from the hospital at the time of the study; that medication administration records were sketchy; and that patients were not observed for adverse effects. A number of other studies conducted by this investigator were reviewed and found to suffer from similar defects. If any of the 27 sponsors of the 82 studies conducted by this investigator had been aware of any serious problems in the conduct of any of these studies, this information was certainly not made known to FDA. We will never know if the sponsors had any knowledge or suspicion of malfeasance, but in those days clinical quality assurance audits were unknown, and the purpose of the contacts of drug company representatives with clinical investigators was to convince the investigators to do studies with their investigational drugs and to prod them to get case report forms completed and submitted as quickly as possible. There was, I am told, also a fear that blowing the whistle on a physician would reflect adversely on the drug company and especially on the number of that company's prescriptions written by the close-knit medical community.

Two clinical investigator inspections were done in 1966, one involving a well-known dermatologist who had done multiple studies in a prison population, and the other involving a New York State

general practitioner who had done multiple studies under INDs. The major finding at the prison was a study reported as a 26 week DMSO study in 20 men, a study which 27 men actually started and which was stopped at 16 weeks with only 15 men still remaining in the study. The New York State GP worked alone in his office and saw all drug study subjects personally. His subjects were extremely reliable and visited his office on the exact protocol day, be it a Sunday or a holiday. A number saw him on 5/4, 6/4/, 7/4, and 8/4 even though 7/4 was Independence Day -- unlikely but possible. However, he had a harder time to explaining how he continued to see study subjects during his extended European vacations, which we documented.

1966 marks another major event in the Bioresearch Monitoring chronology, a memo from then Deputy Commissioner Rankin which called for the development of "a workable system for identifying, making a record of, and investigating investigators ... suspected of submitting questionable results for use in support of applications or petitions to FDA (such as NDAs, INDs, and Food additive petitions), and for use in support of drug advertising." The memo addressed activities not only in the human drug area, but also specifically mentioned animal pharmacology, veterinary products, food additives, and pesticides, thus the scope of Bioresearch Montioring activities was first elucidated.

With the dissolution of the Investigational Drug Branch and the increased awareness of the submission of flawed data came the establishment of the Division of Scientific Investigations in January 1967. The Division consisted of a four person staff, myself, Dr. Frances Kelsey as the Division Director, one consumer safety officer, and a secretary. We undertook to do inspections of the work of clinical investigators, using as a basis the suspect list which had been previously established, the large prison-based drug testing operations, and requests from the IND and NDA reviewers for inspections of the work of suspect physicians. The policy of the time dictated that only a physician was qualified to inspect the work of other physicians, and thus the number of inspections done was limited by my availability and penchant to travel. In the beginning we conducted our inspections in accord with long established policy that called for inspections at reasonable times and in a reasonable manner. "Reasonable times" was interpreted to mean hours of operation, and therefore inspections of physicians were conducted without prior appointment, appearing in the doctor's office and requesting access to the records which were required to be kept. It soon became evident that there was a difference between inspection of a drug manufacturer or of a food processor where the work continued during our inspection and

an inspection of a clinical investigator where we completely disrupted his office and made it difficult for him to see patients and practice medicine, at least during the initial time of our visit. We, therefore, relatively quickly established the operating procedure whereby inspections of clinical investigators were done on appointment, albeit keeping the time between notification and inspection as brief as possible.

Operations in this area remained pretty much unchanged until 1972 which saw two landmarks. The first was the initiation of a survey of the investigational drug work of 15 drug manufacturers, 162 of their clinical investigators, and 70 non-commercial clinical investigators. It was of significance that these inspections were carried out by the FDA field investigator, and did not involve the on-site participation of a physician from headquarters. The survey combined FDA inspection of the monitoring of clinical investigations by the sponsor with inspection of performance of the study by the sponsor's chosen clinical investigators. Its purpose was to determine current practices and procedures of both sponsor and investigators with a view to determining what additional measures were needed to assure the protection of human subjects in clinical trials. Although the survey results showed that grossly violative practices were infrequent, minor deficiencies were frequent. Some unsatisfactory and/or violative performance was found in the areas of patient consent, protocol adherence, study role, records' availability and records' accuracy. The study

showed an obvious inattention to details important to high quality research, that sponsors were not adequately impressing on their investigators their obligations, and were not adequately monitoring ongoing studies with investigational drugs.

While FDA felt that existing regulations made clear the responsibilities of the sponsor to monitor studies, it appeared that those responsibilities were not understood or generally accepted by the sponsors or by the investigators. To clarify this point, the agency asked the Drug Research Board of the Division of Medical Sciences of the National Research Counsel a series of questions in the area of monitoring of clinical investigations. This represents the second landmark of 1972.

The Board-appointed committee clearly supported the agency's contention that the sponsor must assure, through personal contact, the competency of the clinical investigator and laboratory personnel, the adequacy of the facilities for the proposed tasks, and that the investigator understands the nature of the investigational drug and the obligations incurred in undertaking the investigation. The committee also affirmed the responsibility of a sponsor, through periodic site visits, to assure the accuracy of the data, the adequacy of the records, and the adherence to the protocol. The committee affirmed the responsibility of the sponsor to terminate studies as deemed advisable; to relate adverse effects

of drugs discovered in animals to potential effects in man, and to see that patient consent was obtained and an institutional review was undertaken if the study involved institutionalized patients. Finally, it was recommended that the FDA should not be responsible for active monitoring of studies but should look into studies on an occasional basis and when there was reason to question the data.

The General Accounting Office reviewed the data generated in the FDA Special Survey, and in 1976 published a report entitled Federal Control of New Drug Testing is not Adequately Protecting Human Test Subjects and the Public. Also that year, as a result of hearings held by Senator Edward Kennedy, Congressional and Presidential action appropriated to FDA $16.3 million and authorized 600 new positions to carry out expanded activities in the area of Bioresearch Monitoring. As a consequence, Task Forces were established with representatives from each FDA unit, i.e., Drugs, Biologics, Food, Veterinary Medicine, and Radiation Health. The Clinical Investigator/Sponsor Task Force was charged with the development of agency-wide regulations for the conduct of clinical investigators and of sponsor/monitors; the development of agency-wide compliance programs to include enforcement policies, regular inspections of sponsors, monitors, and clinical investigators, and special inspections to audit particular studies; and the development of appropriate organizational structures or mechanisms

and data systems.

With the impetus provided by the GAO report and the infusion of resources, both headquarters and the field hired new personnel to implement the newly christened Bioresearch Monitoring Program. In the drug area this led to the formal establishment of four branches within the Division of Scientific Investigations; one to deal with the activities of clinical investigators, sponsors, and monitors, a second to deal with pre-clinical laboratory studies, a third to deal with institutional review board problems, and the fourth to handle possible criminal cases which developed from the work of the other three. Thus, in 1977 we arrive at the modern era, and our data retrieval systems and our ability to categorize problems and significant events dates to June of that year.

Let me briefly touch on certain other documents that had considerable influence on bioresearch monitoring. The first is a proposed regulation of September 27, 1977 entitled, Obligations of Sponsors and Monitors of Clinical Investigations. The second is a proposed regulation of August 8, 1978 entitled, Obligations of Clinical Investigators of Regulated Articles. These proposed regulations were developed by the Clinical Investigator Task Force. The sponsor/monitor proposal broke entirely new ground, describing not only what was required but also included the authority for FDA

to disqualify a sponsor of a clinical investigation. In my view, the most important item in the proposal was the requirement for quality assurance audits of the work of clinical investigators. In anticipation of finalization of the regulation industry formed QA units, and your presence here is testimonial. The clinical investigator proposal did not break new ground but merely refined and explained the requirements of the then existing regulations.

Like the 1938 Act and the 1962 amendments to it, these regulatory proposals languished through extended comment periods and multiple rewrites, delaying their finalization. Then along came the Reagan era of regulatory relief, and as a result the two proposals never emerged as final regulations. However, with the IND rewrite of March 1987 three significant items from the sponsor/monitor proposal saw the light of day. One recognized the contract research organization as a regulated entity, the second provided that not only authority for the conduct of certain parts of a study could be delegated to the contract research organization, but also permitted that responsibility for those delegated activities could be transferred. The third significant item was in the form a conforming amendment to the NDA regulations which required that with the submission of an NDA the sponsor had to identify each clinical study which was audited or reviewed by the sponsor to verify the accuracy of the case reports submitted. So now, although there is no requirement that clinical audits be done as

was stated in the proposal of 1977, there is certainly a bit of encouragement to do so.

The final story in the fate of the proposed sponsor monitor regulations occurred in January of 1988 when official guidelines for the monitoring of clinical investigations were published, incorporating most of the requirements of the 1977 proposal.

I have now brought you more or less up-to-date with the development of FDA regulations as they apply to clinical investigators and sponsors and monitors, but I have not mentioned anything about the development of our sanctions, i.e., the so called disqualification process.

The original investigational drug regulations that went into effect of February 1963 did recognize that there might be problems with the acceptability of certain clinical studies. You will recall that I talked about a memo of 1961 whereby the New Drug Division was asked to maintain a file of clinical investigators "who have contributed incredible reports to NDAs. . . " This philosophy was reflected in the original Investigational Drug Regulations which stated, "Whenever a sponsor submits to the Commissioner the name of an investigator known to the Commissioner as having repeatedly or deliberately failed to comply with the conditions of these exempting regulations, the Commissioner will notify the sponsor

that the investigator is not entitled to receive investigational use drugs, and such an investigator shall not be supplied any investigational use drugs until adequate assurance is provided to and accepted by the Commissioner that the conditions of the exemption will be met. The Food and Drug Administration will be prepared to confer with the sponsor or the investigator or both on this point."

This was the rule that was followed in our earliest actions against clinical investigators. We were prepared to confer with the investigator. We sent him a letter of about half a page in length and noted that we had inspected specific studies, requested that he familiarize himself with those studies, and asked him to appear to discuss the problems. The investigator would then come to FDA headquarters, which were then in Crystal City in Arlington, Virginia. A brief discussion would be held at a level equivalent to that of the current Office of Drug Evaluation, i.e., equivalent to Dr. Peck's level. The investigator would return home, and soon thereafter he might receive a letter stating that he was ineligible to receive investigational drugs.

It was soon recognized that this process left something to be desired in the way of due process, and in June 1968 our regulations were amended to provide a more structured system. The new regulations required that we furnish the investigator "written

notice of the matter complained of . . . and offer him an opportunity to explain the matter at an informal conference and/or in writing. If the explanation ... was not accepted ... the Commissioner will provide ... an opportunity for an informal hearing on the question of whether the investigator is entitled to receive investigational drugs.." Thus a two level system was established with a truly informal conference at a low level and a truly informal hearing at the Commissioner's level. In practice, the Associate Commissioner for Medical Affairs, John Jennings at the time, was the hearing officer.

This system served quite well, and although the time required to effect a clinical investigator's disqualification increased from approximately six weeks prior to 1968 to about six months, things were going fairly smoothly. However, not content to leave well enough alone, and in pursuit of uniformity in regulatory procedures, in July 1975 the informal hearing with the Commissioner was changed to be a hearing conducted under Part 16 of our regulations. Part 16 Hearings are technically informal but there is one major problem. . .they are handled by LAWYERS. Our informal hearings prior to this time had not necessarily involved lawyers. If a clinical investigator decided to bring a lawyer with him, we would also have a lawyer present, but acting merely in an advisory capacity. One physician even brought his Congressman along, who quickly found that he had to get back to the Hill after it became

evident what sort of information the FDA was presenting. However, with the advent of the Part 16 Hearing, the lawyers took over, the truly informal procedure became for all intents a criminal trial, with the exception that rules of evidence did not apply. There were pre-hearing briefs, opening statements by both parties, presentation of the Prosecution by the FDA, presentation of the Defense by the clinical investigator, post-hearings briefs, and ultimately a decision by the Commissioner. FDA practiced an internal separation of functions whereby various people involved in the matter could not talk to each relative to the matter. We, the Center for Drug Evaluation and Research, had our lawyers. The hearing officer who, for the most part was Dr. Stuart Nightingale, had his team of lawyers. Once he wrote up his decision, it went on to the Commissioner and his team of lawyers, each team having to start from ground zero to learn the details of the case independently. Needless to say the time to effect disqualification of the clinical investigator expanded geometrically, so that what had been a six week process expanded to one that might take in excess of four years.

On top of this, our General Counsel discovered that the regulations provided that when the investigator has "...repeatedly or deliberately submitted false information ... and has failed to furnish adequate assurance (emphasis added) that the conditions of the exemptions will be met ... the Commissioner will notify ..."

In its wisdom our General Counsel decided that the Government had to prove that the investigator had previously lied to the Government in order for us to make a determination that he had failed to provide adequate assurances for the future. Thus came the policy that assurances must be accepted, and the cases of five clinical investigators, who in the opinion of all, including the Commissioner at the time, should have been disqualified were not disqualified because they provided adequate assurances for the future.

After a while we recognized that we did not want our cases to go to hearing no matter how egregious the sins of the investigator were, and the consent agreement process was developed in 1982 so that the matter of an investigator's future use of investigational drugs could be determined at the division level. Each of these agreements is a highly individualized document. There are two general types of agreements. In the first type, the individual agrees to do no further studies of drugs within FDA jurisdiction. In the second type, the individual agrees to some specific restriction of the use of investigational drugs. This restriction might be to limit his studies to Phase III studies. It might be to conduct studies under specific oversight of an individual acceptable to both the physician and to the agency, or it might be any other mutually acceptable representations. In light of the

"adequate assurance" policy we entered into a number of consent agreements that were less stringent than we might otherwise have desired. Finally, with the publication of the IND rewrite in 1987, the offending "adequate assurance" language was deleted, and we are back in the business of holding Part 16 Hearings, but the protracted nature of the process still represents a significant problem.

There is one last area that I want to address -- the FDA inspections of foreign clinical studies.

Before 1975 FDA accepted non-U.S. clinical studies as supportive evidence only; these studies could not be used as one of the "adequate and well controlled studies" on which approval for U.S. marketing was based. In that year FDA policy changed slightly, and the Agency accepted foreign studies as primary evidence, but the drug in question must have been for a major health gain, an uncommon disease, or have had a strikingly favorable benefit/risk ratio. In 1978, Dr. J. Richard Crout first stated that it was the credibility of the data, not their country of origin which should be the determining factor in use of data as primary evidence for drug approval, but it was not until 1981 that the first instance occurred; timolol for prevention of myocardial reinfarction based on Norwegian data. This, however, was not the original approval of the drug for U.S. marketing but was a new

indication for an already marketed drug. In 1982 the NDA rewrite regulations were published as a proposal, but contained the restrictive language of the 1975 policy. However, when these regulations were published in final form in 1985 that language had been removed, and it was established that FDA would accept foreign data as the sole basis for drug approval if they were applicable to the U.S. population and U.S. medical practice, the studies were performed by investigators of recognized competence, the data might be considered valid without the need for an on-site inspection by FDA, or if FDA considered an inspection to be necessary, FDA was able to validate the data through an on-site inspection or other appropriate means.

The FDA has never been able to determine what other appropriate means were sufficient and has not determined criteria for study acceptance without on-site inspection. Thus, it is FDA policy to audit foreign studies which provide the basis for drug approval (including those supporting major supplements) where domestic studies providing this basis do not exist.

As I stand back and look at this historical overview, the thing that strikes me most is the change in focus of our inspectional programs. There has been a slow decrease in our investigator-

targeted for-cause inspections and a corresponding increase in our study-targeted clinical investigator related inspections.

Originally we were out to catch crooks. In 1977, with the formal initiation of the BiMo program we began looking at studies important to the approval of new drugs. With the increasing importance of foreign studies, we have been doing more and more for-cause inspections aimed at validation of submitted data and fewer because of suspicion of malfeasance on part of the clinical investigator. Although I have not previously mentioned it, we are now looking at more and more in vivo bioequivalence studies; again, not to catch crooks, but to determine whether the data submitted were properly obtained and do in fact provide evidence allowing the generic drug subject of the inspection to be marketed. I anticipate that this is the course that we will be following in the foreseeable future.